

## PATENT COOPERATION TREATY

## PCT

REC'D 16 OCT 2003

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference <b>T1566</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/GB 03/ 01302</b>	International filing date (day/month/year) <b>21/03/2003</b>	Priority date (day/month/year) <b>22/03/2002</b>
International Patent Classification (IPC) or national classification and IPC. <b>C07D215/38</b>		
Applicant <b>MERCK SHARP &amp; DOHME LIMITED</b>		


1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This **REPORT** consists of a total of 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT):

These annexes consists of a total of \_\_\_\_\_ sheets.

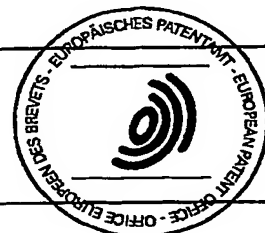
3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Best Available Copy

Date of submission of the demand <b>30/07/2003</b>	Date of completion of this report <b>09/10/2003</b>
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer <b>GELLIE B R</b>  Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)



**I. Basis of the report**

The basis of this international preliminary examination is the application as originally filed.

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability**

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

# PATENT COOPERATION TREATY

# PCT

REC'D 08 JUL 2003
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## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>T1566</b>	<b>FOR FURTHER ACTION</b> <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. <b>PCT/GB 03/ 01302</b>	International filing date (day/month/year) <b>21/03/2003</b>	(Earliest) Priority Date (day/month/year) <b>22/03/2002</b>
Applicant  <b>MERCK SHARP &amp; DOHME LIMITED</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 10 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

**4. With regard to the title,**

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**HETEROROMATIC UREA DERIVATIVES AS VR-1 RECEPTOR MODULATORS FOR TREATING PAIN**

**5. With regard to the abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 03/01302

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D215/38 C07D215/40 C07D217/22 C07D217/24 C07D217/26  
C07D237/28 C07D401/12 C07D401/14 C07D521/00 A61K31/4709  
A61K31/472 A61K31/4725 A61K31/502 A61K31/506 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMCATS 'Online! chemical abstracts service, columbus, ohio, us; XP002244788 order number T0507-0244 & "Enamine Product Listing" 15 November 2001 (2001-11-15), ENAMINE, KIEV 042, 01042, UKRAINE	1,3-6
X,P	DATABASE CHEMCATS 'Online! chemical abstracts service, columbus, ohio, us; XP002244789 order number M-161217 & "Scientific Exchange Product List" 1 January 2003 (2003-01-01), SCIENTIFIC EXCHANGE, INC., CENTER OSSIPPEE, NH, 03814, USA	1,3-6

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

18 June 2003

Date of mailing of the international search report

07/07/2003

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/01302

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>AGARWAL S K ET AL: "Antiparasitic agents: Part XV - Synthesis of 2-substituted 1(3)H-imidazo[4,5-f]isoquinolines as anthelmintic agents"</p> <p>INDIAN JOURNAL OF CHEMISTRY, JODHPUR, IN, vol. 31B, March 1992 (1992-03), pages 177-182, XP009012271</p> <p>Scheme 1, compounds 7 and 8</p> <p>page 179, column 2</p>	1,3-6
X	<p>US 5 508 288 A (FORBES IAN T ET AL)</p> <p>16 April 1996 (1996-04-16)</p> <p>claims 1,7; example 15</p>	1-4,6-8
X	<p>US 4 045 439 A (PRESTON JOHN ET AL)</p> <p>30 August 1977 (1977-08-30)</p> <p>examples 17,24</p>	1-3,6
X	<p>HONMA TERUKI ET AL: "Structure-Based Generation of a New Class of Potent Cdk4 Inhibitors: New de Novo Design Strategy and Library Design"</p> <p>JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 44, 2001, pages 4615-4627, XP002220243</p> <p>ISSN: 0022-2623</p> <p>page 4624, column 1, line 15 - line 23; figure 3; examples 4,14B; table 2</p>	1-3,5,6
X	<p>DE 11 57 626 B (FARBWERKE HOECHST AG)</p> <p>21 November 1963 (1963-11-21)</p> <p>examples 1-10</p>	1,3,5,6
X	<p>DE 583 207 C (I G FARBENINDUSTRIE AKT GES)</p> <p>30 August 1933 (1933-08-30)</p> <p>examples 1,2,5-7,9</p>	1-4,6,8
X	<p>WO 93 24458 A (PFIZER ;HAMANAKA ERNEST S (US)) 9 December 1993 (1993-12-09)</p> <p>cited in the application</p> <p>claims 1-5,7,9; examples 77,79,82,87</p>	1-3,5-8
X	<p>PORADOWSKA H ET AL: "Phenylloquinoline derivatives of urea "</p> <p>ROCZNIKI CHEMII ANNALES SOCIETATIS CHIMICAE POLONORUM, XX, XX, vol. 49, 1975, pages 1577-1580, XP009012273</p> <p>ISSN: 0035-7677</p> <p>examples 2-8; table 1</p>	1-3,5,6

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 03/01302

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PORADOWSKA H ET AL: "Phenylquinoline derivatives of thiourea" POLISH JOURNAL OF CHEMISTRY, POLISH CHEMICAL SOCIETY, XX, vol. 53, 1979, pages 1895-1900, XP009012274 examples 2-8; table 1 ---	1,3,5,6
X	MUSSER J H ET AL: "Synthesis and Antilipolytic Activities of Quinolyl Carbanilates and Related Analogues" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 30, no. 1, 1987, pages 62-67, XP002244786 ISSN: 0022-2623 page 66, column 1; figure 1; example 13; table 1 ---	1
X	JOSHI K C ET AL: "Chemical Constituents of Clerodendron infortunatum Linn. and Ficus racemosa Linn." JOURNAL OF THE INDIAN CHEMICAL SOCIETY, THE INDIAN CHEMICAL SOCIETY, CALCUTTA, IN, vol. 54, 1977, pages 1104-1105, XP009012272 ISSN: 0019-4522 examples 1-50 ---	1,3,5,6
X	WO 94 14801 A (SMITHKLINE BEECHAM PLC ;FORBES IAN THOMSON (GB); MARTIN ROGER THOM) 7 July 1994 (1994-07-07) claims 1-4,7,8; examples 8,11,12 ---	1,3,5-8
X	WO 00 26203 A (ISACCHI ANTONELLA ;TRAQUANDI GABRIELLA (IT); VILLA MANUELA (IT); V) 11 May 2000 (2000-05-11) claims 1,6,13,16; example 189 ---	1-3,5-8
X	DE 25 02 588 A (TROPONWERKE DINKLAGE & CO) 29 July 1976 (1976-07-29) page 25; claims 1,3; examples 39-42 ---	1-3,5-10
Y	WO 02 08221 A (BAKTHAVATCHALAM RAJAGOPAL ;DESIMONE ROBERT W (US); NEUROGEN CORP ( ) 31 January 2002 (2002-01-31) cited in the application page 4, line 12 - line 18; claims 1,187,188,194-196 ---	1-10
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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 03/01302

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SONDHI S M ET AL: "SYNTHESIS AND ANTICANCER, ANTIINFLAMMATORY, AND ANALGESIC ACTIVITY EVALUATION OF SOME SULFA DRUG AND ACRIDINE DERIVATIVES" MONATSCHEFTE FUR CHEMIE, SPRINGER VERLAG. WIEN, AT, vol. 131, no. 5, 2000, pages 511-520, XP001088543 ISSN: 0026-9247 page 517, paragraph 4 -page 518, paragraph 3; example 7 ---	1-10
Y	LEE ET AL: "N-(3-Acyloxy-2-Benzylpropyl)-N'-Dihydroxy tetrahydrobenzazepine and Tetrahydroisoquinoline Thiourea Analogues as Vanilloid Receptor Ligands" BIOORGANIC & MEDICINAL CHEMISTRY, OXFORD, GB, vol. 9, 2001, pages 1713-1720, XP002244787 ISSN: 0960-894X cited in the application page 1714, column 1, paragraph 3 -column 2, paragraph 2 page 1717, column 1, paragraph 3 -column 2, paragraph 1; figure 2; examples 18,27,28 ---	1-10
P,Y	WO 03 014064 A (BAYER AG ;FREITAG JOACHIM (DE); MEIER HEINRICH (DE); LOWINGER TIMO) 20 February 2003 (2003-02-20) page 10, line 11 - line 19; claims 1,14,16,17; tables 1,3-6,8 -----	1-10

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 03/01302

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1-3(part), 5-10(part)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.



## INTERNATIONAL SEARCH REPORT

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

### Continuation of Box I.1

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

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### Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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### Continuation of Box I.2

Claims Nos.: 1-3(part),5-10(part)

Present claims 1-3, 5-10 (in part) relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds in which the fused "A=B-D=E"-heterocycle of formula (I) is either quinoline, isoquinoline or cinnoline, thereby including all of the given examples.

It is noted that claim 1 of the application refers to prodrugs. "Prodrugs" is a functional definition which attempts to define a chemical compound in terms of a result to be achieved. This is not allowable (Article 6 PCT). "Prodrugs" is a functional definition without a specific technical guidance for the selection of the suitable derivatives in the description and without proven general knowledge to show which derivatives are suitable prodrugs. The term could be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants, a situation, which imposes an undue burden on the skilled person (insufficient disclosure in the sense of Article 5 PCT) even when simple in vivo or in vitro tests are available to determine whether or not a particular compound is covered by the claims. Claim 1 has therefore been searched incompletely, omitting the term "prodrug".

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a

## INTERNATIONAL SEARCH REPORT

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 03/01302

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5508288	A	16-04-1996	AU 3641193 A EP 0630373 A1 WO 9318028 A1 JP 7504429 T MX 9301336 A1 ZA 9301713 A	05-10-1993 28-12-1994 16-09-1993 18-05-1995 01-10-1993 22-09-1994
US 4045439	A	30-08-1977	GB 1472766 A AU 8610175 A BE 835165 A1 DD 123339 A5 DE 2550179 A1 DK 500775 A FI 753113 A FR 2290209 A1 IN 141110 A1 JP 51070778 A NL 7512958 A NO 753718 A SE 7512447 A SE 7807225 A US 4085103 A ZA 7506710 A	04-05-1977 05-05-1977 30-04-1976 12-12-1976 13-05-1976 08-05-1976 08-05-1976 04-06-1976 22-01-1977 18-06-1976 11-05-1976 10-05-1976 10-05-1976 26-06-1978 18-04-1978 27-10-1976
DE 1157626	B		NONE	
DE 583207	C	30-08-1933	NL 34898 C US 2042023 A	26-05-1936
WO 9324458	A	09-12-1993	AU 4028393 A BG 99188 A BR 9306421 A CA 2134359 A1 CN 1080919 A EP 0642498 A1 FI 932423 A HR 930931 A1 HU 64303 A2 JP 7503737 T MX 9303100 A1 NO 944530 A OA 10114 A PL 299082 A1 SK 142694 A3 WO 9324458 A1 US 6001860 A	30-12-1993 28-07-1995 15-09-1998 09-12-1993 19-01-1994 15-03-1995 29-11-1993 30-06-1997 28-12-1993 20-04-1995 30-06-1994 25-11-1994 18-12-1996 05-04-1994 07-06-1995 09-12-1993 14-12-1999
WO 9414801	A	07-07-1994	WO 9414801 A1	07-07-1994
WO 0026203	A	11-05-2000	AU 1044700 A BR 9914868 A CA 2347060 A1 CN 1325390 T CZ 20011413 A3 WO 0026203 A1 EP 1124811 A1 HU 0104167 A2 JP 2002528538 T	22-05-2000 03-07-2001 11-05-2000 05-12-2001 12-09-2001 11-05-2000 22-08-2001 28-03-2002 03-09-2002

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No  
PCT/GB 03/01302

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0026203	A		NO 20012058 A PL 347506 A1 SK 4752001 A3	28-06-2001 08-04-2002 05-02-2002
DE 2502588	A	29-07-1976	DE 2502588 A1	29-07-1976
WO 0208221	A	31-01-2002	AU 8066701 A EP 1301484 A2 WO 0208221 A2 US 2002132853 A1	05-02-2002 16-04-2003 31-01-2002 19-09-2002
WO 03014064	A	20-02-2003	JP 2003055209 A WO 03014064 A1	26-02-2003 20-02-2003